Early role for IL-6 signalling during generation of induced pluripotent stem cells revealed by heterokaryon RNA-Seq.

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Public Summary:
Molecular insights into somatic cell reprogramming to induced pluripotent stem cells (iPS) would aid regenerative medicine, but are difficult to elucidate in iPS because of their heterogeneity, as relatively few cells undergo reprogramming (0.1-1%; refs ,). To identify early acting regulators, we capitalized on non-dividing heterokaryons (mouse embryonic stem cells fused to human fibroblasts), in which reprogramming towards pluripotency is efficient and rapid, enabling the identification of transient regulators required at the onset. We used bi-species transcriptome-wide RNA-seq to quantify transcriptional changes in the human somatic nucleus during reprogramming towards pluripotency in heterokaryons. During heterokaryon reprogramming, the cytokine interleukin 6 (IL6), which is not detectable at significant levels in embryonic stem cells, was induced 50-fold. A 4-day culture with IL6 at the onset of iPS reprogramming replaced stably transduced oncogenic c-Myc such that transduction of only Oct4, Klf4 and Sox2 was required. IL6 also activated another Jak/Stat target, the serine/threonine kinase gene Pim1, which accounted for the IL6-mediated twofold increase in iPS frequency. In contrast, LIF, another induced GP130 ligand, failed to increase iPS frequency or activate c-Myc or Pim1, thereby revealing a differential role for the two Jak/Stat inducers in iPS generation. These findings demonstrate the power of heterokaryon bi-species global RNA-seq to identify early acting regulators of reprogramming, for example, extrinsic replacements for stably transduced transcription factors such as the potent oncogene c-Myc.

Scientific Abstract:
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